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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/042,746	11/20/2002	Daniel J. Drucker	016777-0528	7720

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EXAMINER	
HARLE, JENNIFER I	

ART UNIT	PAPER NUMBER
1654	

DATE MAILED: 02/14/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/042,746	DRUCKER, DANIEL J.	
	Examiner	Art Unit	
	Jennifer I. Harle	1654	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *20 November 2002*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *18-26* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *18-26* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *03/20/03*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Claims 18-26 are pending. Claims 1-17 were deleted by Preliminary Amendment.

Claim Rejections - 35 USC § 112

1. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

2. Claims 18 and 20, 21-26 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Claims 8 and 20, 21-26 are enabled for rat GLP-2 and homologous GLP-2 for other vertebrate mammals. The examiner is interpreting "comprising GLP-2" to include analogs and non-vertebrate forms of GLP-2, as comprising could encompass any form of GLP-2 and analogs are included withinknown forms of GLP-2, e.g. Rat (D-Alanine), Rat (2-glycine), Rat (2-Valine). However, Applicant is not enable for GLP-2 from non-vertebrate GLP-2 animals, i.e. amphiuma tridactylum (salamander) lophium americanus (angler fish), petromyzon marinus (an ancient vertebrate lacking a calcified skeleton and teeth), or rana catesbeiana (American bullfrog) for example. The screening assay itself is not in contention. A screening assay only needs the possibility of finding a composition, that can improve function of gastrointestinal tissue to be enabled. Thousands of compounds might be unsuccessfully screened for such a compound yet the screen itself would still be fully enabled. That is one could practice the screen albeit unsuccessfully.

Thus, the availability of a screen is no guarantee of success in finding a pharmaceutical compound that will improve the gastrointestinal tissue in a patient in need thereof to enhance nutritional absorption of the small intestine. It is the subject of considerable original research to provide such compounds. The experimentation is undue and not merely routine when the decision on which compounds to test are limited in guidance by the disclosure. In the instant case, there is guidance only to rat GLP-2 and its homologues, including ox GLP-2, porcine, degu, bovine, guinea pig, hamster human rainbow trout and chicken – none of which are non-vertebrate. Applicant states that his preferred preference is based upon the human GLP-2 and conserved substitutions and then non-conserved substitutions at 13, 16, 19, 27, and 28 and then proceeds 13, 19-20, 27-28 and further to include in the non-conserved substitutions 2, 5, 7-10, 12, 17, 21-24, 26, 29-33. If one takes all of the non-conserved substitutions together the non-conserved substitutions are 2, 5, 7-10, 12-13, 17, 19-24, 26-33. As human GLP-2 only has 33 amino acids, that leaves only 9 of the 33 amino acids that would preferably not be non-conservatively substituted, i.e. over 72% are non-conservatively substituted at a minimum. Specification, pp. 8-9. Additionally Applicant states that any non-conservative substitutions can be made any position in which alanine-scanning mutagenesis reveals some tolerance for mutation in that substitution of an amino acid **residue** with alanine does not destroy all intestinotrophic activity. Specification, pg. 9. However, no guidance is provided on the meaning of non-conservative amino acids, which ones to substitute where or examples of substitutions within the GLP-2 peptides, with the exception of the naturally occurring GLP-2 peptides. Only rat was "substituted" and that was at the amino and carboxy terminus with Arg residues. It is noted that even their preferred embodiment was not tested with the rats or mice. Inventions

targeted for human therapy bear a heavy responsibility to provide supporting evidence because of the unpredictability in biological responses to therapeutic treatments. The standard of enablement is higher for such inventions because of effective treatments for disease conditions are relatively rare, and may be unbelievable in the absence of strong supporting evidence. Claims drawn to pharmaceutically acceptable compositions and methods of administering compounds to humans generally require supporting evidence because of the unpredictability in biological response to therapeutic treatments. The instant specification is limited to the addition of amino acid ARG to rat GLP-2 and degu GLP-2.

Moreover, with regards to the effect of amino acid substitution in a peptide or protein, the art is unpredictable and given that Applicant is substituting a.

Rudinger[1] teaches that, "The significance of particular amino acids and sequences for different aspects of biological activity cannot be predicted *a priori* but must be determined from case to case by painstaking experimental study." (Page 6).

SIGMA[2] states that with regards to design of peptide sequences that, "Even for relatively short sequences, there are essential and non-essential (or less important) amino acid residues, although the relative importance of the individual amino acid residues is not always easy to determine." (Page 1). SIGMA further describes what effect some substitutions *may have*, rather than what effect they *will have* on hydrophobicity, secondary structure (which will affect tertiary and quaternary structure), and solubility.

With regards to prediction of the native conformation of a protein (structure), the art is unpredictable.

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[1] J Rudinger. In: Peptide Hormones, JA Parsons, Ed. (1976) 1-7.

Berendsen[3] states, "The prediction of the native conformation of a protein of known amino acid sequence is one of the great open questions in molecular biology and one of the most demanding challenges in the new field of bioinformatics." (Page 642). Berendsen states that, :Folding to the stable native state [computationally] has not (yet) occurred, and the simulations do not contain any relevant statistics on the process. The real protein will fold and refold hundreds to thousands of times until it stumbles into the stable conformation with the lowest free energy. Because this hasn't happened (and couldn't happen) in the simulations, we still cannot be sure of the full adequacy of the force field. (Page 642).

Further, the effects of a single amino acid substitution can have substantial effects on proteins in structure and/or function and are exemplified by the difference between hemoglobin (Hb) and abnormal hemoglobins, such as sickle-cell hemoglobin (HbS). Voet[4] teaches that the mutant hemoglobin HbE [Glu B8(26)β → Lys] has, "no clinical manifestations in either heterozygotes or homozygotes." (Page 235). Further, Hb Boston and Hb Milwukee both have single point mutations which result in altered binding affinity and ineffective transfer from the Fe(III) to Fe(II) oxidation state. Conversely, a single point mutation in Hb Yakima results in increased oxygen binding by the heme core, and in Hb Kansas, the mutation causes the heme center to remain in the T state upon binding oxygen (rather than structurally rearranging to the R state). (Page 236).

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[2] SIGMA. Designing Custom Peptides. http://www.sigma-genosys.com/peptide_design.asp (Accessed 12/16/2004). 2 pages.
[3] HJC Berendsen. A Glimpse of the Holy Grail? Science (1998) 282. 642-643.
[4] D Voet and JG Voet. Biochemistry, 2nd Edition.(1995). 235-241.

HbS is a single point mutation, Val → Glu A3(6)β (Page 236), which results in deformation and rigidity of the red blood cell. The mutation also provides protection against most malarial strains.

Given that one could not determine the structure of a protein computationally, and that the effect of amino acid substitution is unpredictable, it flows logically that one would be unduely burdened with experimentation to determine the effect of amino acid substitution(s) in a peptide or protein, with regards to structure, function, or physical/chemical properties.

Claim Rejections - 35 USC § 102

1. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (e) the invention was described in a patent granted on an application for patent by another filed in the United States before the invention thereof by the applicant for patent, or on an international application by another who has fulfilled the requirements of paragraphs (1), (2), and (4) of section 371(c) of this title before the invention thereof by the applicant for patent.

The changes made to 35 U.S.C. 102(e) by the American Inventors Protection Act of 1999 (AIPA) and the Intellectual Property and High Technology Technical Amendments Act of 2002 do not apply when the reference is a U.S. patent resulting directly or indirectly from an international application filed before November 29, 2000. Therefore, the prior art date of the reference is determined under 35 U.S.C. 102(e) prior to the amendment by the AIPA (pre-AIPA 35 U.S.C. 102(e)).

2. Claims 21-26 are rejected under 35 U.S.C. 102(e) as being anticipated by Matsuno, et al. (US 5,432,156).

Matsuno discloses an analog of GLP-2, glicentin, by definition as it has intestinotrophic activity an the analog is structurally altered relative to such vertebrate GLP-2, i.e. human, by at least one, i.e. all, amino acids have been either added, deleted, or substituted or by incorporation of an amino acid blocking group to enhance the nutritional absorption of the small intestine. See cols. 3-8. No specific definition of an analog is provided in the specification, preferred emobodiments, including conservative and nonconservative substitutions are set forth but are not set forth as definitions for the definition of an analog. See Specification pp. 8-10 ("various vertebrate forms of GLP-2 include, **for example**...", Analogs of vertebrate GLP-2 **can be** generated using standard techniques and **can be** assessed for intestinotrophic activity, all according to the guidance provided herein. ... wherein one or more amino acid residues **are conservatively** substituted for another amino acid residue, ... The invention also encompasses non-conservative substitution of amino acids in any vertebrate GLP-2 ... Thus, under, this standard, the amino acid postions which vary in mammals and which preferably may be substituted with non-conservative residues ... The additional amino acid residues which vary in vertebrates and which may be substituted with non- conserved residues ... Alternatively, non-conservative substitution may be made at any position fin which alanine-scanning mutagenesis reveals some tolerance for mutation in that substitution ..." – noting that they do not have to be generated according to these techniques or assessed in this manner).

Double Patenting

3. The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed.

Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970);and, *In re Thorington,* 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

4. Claims 18-26 are rejected under the judicially created doctrine of double patenting over claims 2, 4, 11, 17, 25, 39,57, 63, 66-68, 48, 50, of U. S. Patent No. 5,990,077 since the claims, if allowed, would improperly extend the "right to exclude" already granted in the patent.

The subject matter claimed in the instant application is fully disclosed in the patent and is covered by the patent since the patent and the application are claiming common subject matter, as follows: Although the conflicting claims are not identical, they are not patentably distinct from each other because the difference between the two invention is the scope of the GLP-2 analogs and are directed to methods of treating the small intestine, which would necessarily increase nutritional uptake.

Furthermore, there is no apparent reason why applicant was prevented from presenting claims corresponding to those of the instant application during prosecution of the application which matured into a patent. See *In re Schneller*, 397 F.2d 350, 158 USPQ 210 (CCPA 1968). See also MPEP § 804.

The examiner notes that there are a plethora of Applications with claims direct to GLP-2 peptides and their analogs with potentially overlapping subject matter with the same inventive entity in process for example 10/293941, US Patent 6,18,201, US Patent 5789379, 10/829201, 10/419150, US Patent 6586399, among others to enhancing functioning of the large

intestine/upper gastrointestinal tract, and GLP-2 analogs. Applicant(s)/Assignee are requested to review their filings and file any and all appropriate terminal disclaimers.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Jennifer I. Harle whose telephone number is (571) 272-2763. The examiner can normally be reached on Monday through Thursday, 6:30 am to 5:00 pm,.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Bruce Campell can be reached on (571) 272-0974. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Jennifer I. Harle
Examiner
Art Unit 1654

February 7, 2005